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Treatment of Multifocal Lymphoma of Bone With Intensified Promace-Cytabom Chemotherapy and Involved Field Radiotherapy

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Primary bone involvement is an unusual extranodal presentation of non-Hodgkin lymphoma (NHL). The optimal treatment for this entity has not been determined. While solitary bone lymphomas can be eradicated with local radiation in 50% of patients, distant relapses occur frequently, and the treatment of patients with multifocal osseous disease, or those presenting with associated soft tissue invasion or adenopathy is even less satisfactory. Over a 4-year period, nine patients with multifocal bone lymphoma were treated with intensified versions of the ProMACE-CytaBOM regimen and involved-field radiation. Seven patients had diffuse large cell histology and two patients had diffuse mixed type. Seven patients survived event-free at a median follow-up of 2.3 years (range .5–3.5). In most survivors, there was little or no change in the abnormal radiographic bone findings despite the clinical response to therapy. In one patient, magnetic resonance imaging (MRI) established that bone infarction rather than relapse of lymphoma was the cause of a new lytic bone lesion that developed during treatment. Am. J. Hematol. 58:1–7, 1998. © 1998 Wiley-Liss, Inc.

Key words: lymphoma; bone; chemotherapy; radiotherapy; dose-escalation

INTRODUCTION

Primary lymphoma of bone, first described by Oberling (1928) [1] and in depth by Parker and Jackson (1939) [2] constitutes about 5% of extranodal non-Hodgkin lymphomas and about 5% of primary bone tumors [3,4]. The optimal treatment for this type of lymphoma has not yet been defined due to its rarity and the ongoing evolution of treatment practices. In the largest reported series of patients with bone lymphoma, 422 patients evaluated at the Mayo Clinic from 1907 to 1982 were classified according to whether bone involvement was solitary (Group 1), multifocal (Group 2), or associated with soft tissue or nodal invovlement (Groups 3 and 4) [5]. The 5-year Kaplan-Meier survivals were 58% for Group 1 patients, 42% for Group 2 patients, and 22% for Groups 3 and 4 patients. Treatment strategies included radiotherapy, surgery plus radiotherapy, and radiotherapy plus chemotherapy. No significant differences in survival were noted between patients who received these alternative treatments.

Based on the inferior outcome for patients with multifocal bone involvement, soft tissue involvement, or adenopathy (Groups 2, 3, and 4), nine patients who exhibited one or more of these adverse clinical characteristics were treated with intensified versions of the ProMACE-CytaBOM regimen (seven patients) or the standard-dose version (two patients > 75 years of age) followed by involved-field radiotherapy when feasible.

In five patients the intensified version of ProMACE-CytaBOM consisted of doxorubicin at a dose of 50

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TABLE I. Treatment Characteristics*

UN	Pred (60 mg/m^2 × 14 days) (%)	Doxo (25 mg/m^2) (%)	Cyclo (650 mg/m^2) (%)	Etop (120 mg/m^2) (%)	Cyta {300 mg/m^2) (%)	Bleo (5 mg/m^2) (%)	Vinc (1.4 mg/m^2) (%)	Mtx (120 mg/m^2) (%)	No. of cycles	GF support (+/−)	XRT dose (Gy)	EFS (years)
1	81	200	175	175	163	88	100	100	8	+	36	3.5+
2	100	200	200	200	157	100	100	200	7	+	30–36	3.2+
3	39	175	100	100	100	100	100	100	8	+	40	3.5+
4	50	163	100	100	87	87	81	100	8	+	—	2.3+
5	50	200	100	100	100	100	100	100	6	−	40	1.0+
6	43	200	100	100	100	100	100	100	6	−	41	.8+
7	50	100	100	100	100	100	100	100	8	+	—	.5+
8	50	188	100	100	100	100	100	100	8	−	—	.9
9	50	100	96	92	100	100	33	100	6	+	—	.5

*Pred = prednisone; doxo = doxorubicin; cyclo = cyclophosphamide; etop = etoposide; cyta = cytarabine; bleo = bleomycin; vinc = vincristine; mtx = methotrexate. The standard doses of the drugs are given at the top of each column. Shown are the percentages of the standard doses given to the patients during each cycle, averaged over their treatment courses. Prednisone was generally given for 7 days rather than 14 days to reduce the risk of avascular necrosis of the hips, accounting for the low percentages in this column. GF refers to administration of hematopoietic growth factors (G-CSF or GM-CSF) during the treatment period. XRT is the total dose of involved field radiotherapy; one patient (UN-2) received different doses to different sites of diseases. EFS is the event-free survival calculated from the start of treatment.

mg/m^2 (standard = 25 mg/m^2) while two patients received escalated doses of doxorubicin, cyclophosphamide, etoposide, cytarabine, and methotrexate. The rationale for adopting these regimens was as follows: Lower doxorubicin doses (⩽75% scheduled dose) may be associated with an inferior survival in patients treated with CHOP chemotherapy for large cell lymphomas [6,7]. The equivalent survivals for patients who were randomized to receive CHOP, ProMACE-CytaBOM, or two other chemotherapy regimens [8], suggested that the inclusion of etoposide, cytarabine, bleomycin, and methotrexate in the standard ProMACE-CytaBOM regimen may compensate for the decreased dose of doxorubicin (25 mg/m^2) included in this regimen. Doubling the dose of doxorubicin to equal that given with standard CHOP (50 mg/m^2) could, therefore, augment the activity of this treatment regimen. Furthermore, a recently published phase I trial of ProMACE-CytaBOM chemotherapy for untreated diffuse lymphoma demonstrated that the doses of cyclophosphamide, doxorubicin, etoposide, and cytarabine could be safely doubled when combined with hematopoietic growth factor support [9]. The complete remission (CR) was 66% in this trial and 92% of complete responders remained in CR for a median of 3.6 years.

METHODS

Diagnostic Methods

All patients had lymphoma limited to or predominantly involving multiple bone sites. Local soft tissue extension and limited adenopathy were considered to be secondary sites of disease. Routine staging studies included CT scans of the chest and abdomen, a radionuclide bone scan, bilateral iliac crest bone marrow biopsies, and MRI or CT scans of the involved bones. Pulmonary function tests and radionuclide ventriculograms were performed prior to treatment and repeated after four or five cycles of therapy.

Treatment Methods

As shown in Table I, patients were treated with escalated versions of standard dose ProMACE-CytaBOM chemotherapy. For the two patients >75 years of age (UN-7, UN-9), standard-dose therapy was given while all others received increased doses of doxorubicin. In addition, one patient (UN-2) was enrolled in the phase II portion of an Eastern Cooperative Oncology Group study, and received escalated doses of doxorubicin, cyclophosphamide, etoposide, cytarabine, and methotrexate. A second patient (UN-1) received similar treatment. Double-strength trimethoprim/sulfamethoxazole was given twice weekly to prevent pneumocystis pneumonia.

Involved field radiotherapy (30–40 Gy) was administered to five patients with multifocal bone involvement. Two patients (UN-4, UN-7) did not receive radiation because their disease was too widespread. One patient (UN-9) relapsed too quickly and one patient developed lymphoma in the calcaneus (UN-8) where he had received maximal radiation 40 years earlier for an undefined tumor.

Statistical Methods

Survival was calculated from the start of chemotherapy. An event was defined as disease relapse or progression based on serial clinical and radiographic studies,

TABLE II. Patient Characteristics*

UN	Age (gender)	Bone sites	Soft tissue (+/−)	Adenopathy	BM involved (+/−)	Time from Sx→Dx (months)	LDH (≥1.2 × NML)
1	19 (f)	Pelvis, L3	+	+	+	20	−
2	31 (m)	Femur, spine, ribs	−	++	+	9	−
3	51 (m)	Both femurs	−	−	−	9	−
4	59 (f)	Diffuse	−	++	+	18	−
5	54 (m)	Iliac, femur	+	+	−	6	+(1.7)
6	26 (m)	Femur, knee	+	−	−	4	−
7	76 (f)	Skull, femurs	+	+	+	6	−
8	52 (m)	Calcaneus, rib	+	−	+	12	−
9	79 (f)	Iliac, humerus, femurs, vertebrae	−	−	−	<1	−

*Soft tissue refers to the presence or absence of local soft tissue invasion. For adenopathy: + = 1–2-cm nodes; ++ = 2–5-cm nodes. BM, bone marrow involvement. Time refers to time elapsed from symptom onset (Sx) to definitive diagnosis (Dz). LDH is the level of serum lactate dehydrogenase just prior to the start of treatment, expressed as a multiple of the upper limit of the normal range.

development of a secondary life-threatening malignancy, or death from any cause. The event-free survival curve was calculated by the method of Kaplan and Meier [10].

Histologic and Immunohistological Methods

Biopsy material was formalin fixed and if necessary decalcified in a mixture of formaldehyde and formic acid (Decalcifer, Surgipath, Richmond, IL) prior to paraffin embedding and tissue sectioning. Sections for hematoxylin and eosin staining as well as immunohistochemistry were cut at 5 μ and mounted on poly-L-lysine-coated (PLL) slides. Immunohistochemistry on paraffin-embedded material for immunophenotyping was performed on reprsentative samples of the tumors by the biotin-streptavidin method [11]. The antibodies utilized included L-26 (CD-20), (pan-B-cell marker, 1:250 dilution), and DF-T1 (CD-43), (pan-T-cell marker, 1:800 dilution), (Dakopatts, Carpinteria, CA). Tumors were assigned to either the B-cell or T-cell lineage if the cytologically abnormal, malignant-appearing cells clearly stained with one of these antibodies and not the other. If the staining was equivocal, or if both of the antibodies stained the abnormal population of cells, then the lineage of the tumor could not be determined.

RESULTS

Clinical and Radiologic Findings

The clinical characteristics of the nine patients are summarized in Table II. The median age of the patients was 52 (range 19–79). Presenting symptoms included bone pain (n = 9) and visible soft tissue swelling (n = 2). Four patients also presented with pathologic fractures of the femurs (2) or humerus (1), which required surgical pinning, and one patient had a fracture of the calcaneus. The median time from symptom onset to diagnosis was 9 months (range 1–20). One patient with widespread bone involvement had pancytopenia at diagnosis while five others had mild degrees of anemia (Hct = 29–37%). The affected bones usually exhibited a lytic or a mixed lytic and sclerotic appearance on plain films and CT scans. MRI scans of affected bones revealed a diminished signal intensity on T1-weighted images and a bright signal intensity on T2-weighted images.

Pathologic Findings

Table III contains a summary of the pathological results. Seven patients had diffuse large cell lymphoma and two had diffuse mixed cell type. Tumor necrosis and reactive marrow fibrosis were commonly observed. Five of five specimens obtained from needle cores were distorted by crush artifact while only two of four specimens obtained by open curetting had this feature. Four patients had B-cell lymphomas, two had T-cell phenotypes, and three had lymphomas of undetermined lineage.

Treatment

Treatment was well tolerated; only one patient required hospitalization (UN-2) for painful stomatitis involving the tongue. No significant decreases in pulmonary function or left ventricular ejection fraction were observed during the treatment and follow-up phases.

TABLE III. Pathology Results*

UN	Histology (cell type)	Tumor necrosis	Crush artifact	Marrow space fibrosis	Type of biopsy	Tumor cell lineage	Bone resorption
1	Diffuse large	++	++	++	Needle core	B-cell	+/−
2	Diffuse large	−	+	+	Needle core	T-cell	−
3	Diffuse mixed	+	+	+/−	Curettings	(?)	−
4	Diffuse large (immunoblastic)	++	−	++	Curettings	B-cell	++
5	Diffuse large	+/−	++	++	Needle core	(?)	++
6	Diffuse mixed	−	+	++	Needle core	Probable T-cell	−
7	Diffuse large	+	+	++	Needle core	B-cell	−
8	Diffuse large	++	+	+	Curettings	(?)	++
9	Diffuse large	++	−	+/−	Curettings	B-cell	++

*Shown are the pathological findings for the bone biopsy specimens. +/− = focal feature; + = easily identified feature; ++ = prominent feature; (?) = lineage indeterminate.

Survival and Follow-Up

The 3-year Kaplan-Meier event-free survival was 73% (95% confidence interval = 41–100%) (Fig. 1). Two patients relapsed: Patient UN-8 relapsed in the calcaneus 0.9 years after the start of therapy; an amputation of the foot and ankle was needed to promote healing and disease control. The marrow involvement in this patient cleared after therapy, however, the patient later developed recurrent disease in the lungs and in the amputation stump. Patient UN-9 developed a new sternal mass shortly after completion of chemotherapy, which did not respond to further chemotherapy or radiotherapy.

While follow-up radiographic studies often showed evidence of a response to therapy, some abnormal radiographic findings remained stable despite continued clinical improvement. For example, serial CT scans of the diseased hemipelvis of the longest surviving patient (UN-1) showed persistent but stable abnormalities of bone architecture (Fig. 2). The associated soft tissue mass completely resolved.

In addition, the development of new ''lytic'' areas on plain films or CT scans did not always signify disease relapse. Figure 3 depicts a plain film interpreted to show new lytic lesions consistent with disease relapse in a patient (UN-2) who presented with new knee pain during therapy. The MRI scan later clarified the diagnosis to be bone infarcts in the distal femur and proximal tibia.

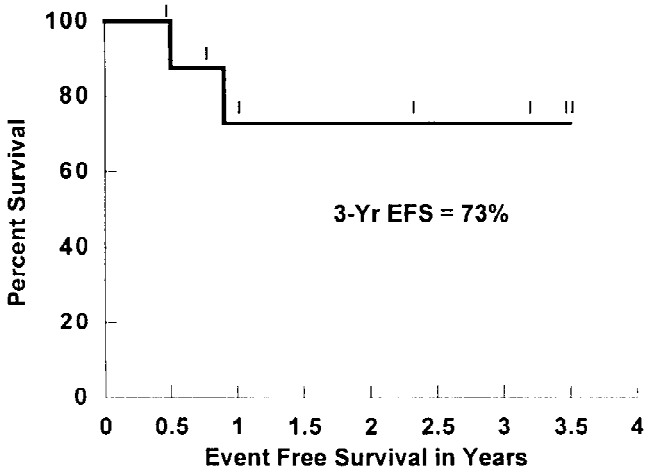

Fig. 1. Kaplan Meier event-free survival for the nine patients. Tick marks indicate the duration of survival for the seven censored (surviving) patients.

DISCUSSION

Extranodal involvement of non-Hodgkin lymphoma (NHL) is associated with an inferior outcome from treatment [12]. While dissemination to bone is not unusual in advanced-stage NHL, primary bone lymphoma constitutes only about 5% of extranodal NHL and may exhibit a distinct clinical course. Local (radiation field) recurrences are rare in patients with solitary bone lesions who received radiotherapy alone or radiotherapy combined with chemotherapy [5,13–17]. However, marginal or distant relapses occurred in about 50% of patients who received radiation alone, suggesting that combined modality treatment may be preferred for certain subgroups of patients [17].

Several pathologic and clinical factors appeared to correlate with inferior outcomes for patients with bone lymphoma including the presence of large non-cleaved cells or nuclear pleomorphism in the biopsy, disease dissemination, and soft tissue invasion. The 5-year event-free survival (EFS) was 69% for patients with tumors composed mainly of cleaved cells, 13% for those with non-cleaved cells, and 0% for the pleomorphic subgroup [13]. However, one report of three patients with CD30+ (Ki-1 +) anaplastic large cell lymphoma of bone, a distinct pleomorphic subtype, showed durable complete responses to chemotherapy with or without radiation [18].

The large study by Ostrowski et al. [5] demonstrated the adverse effects of multifocal involvement, dissemination to lymph nodes, and soft tissue invasion. Simi-

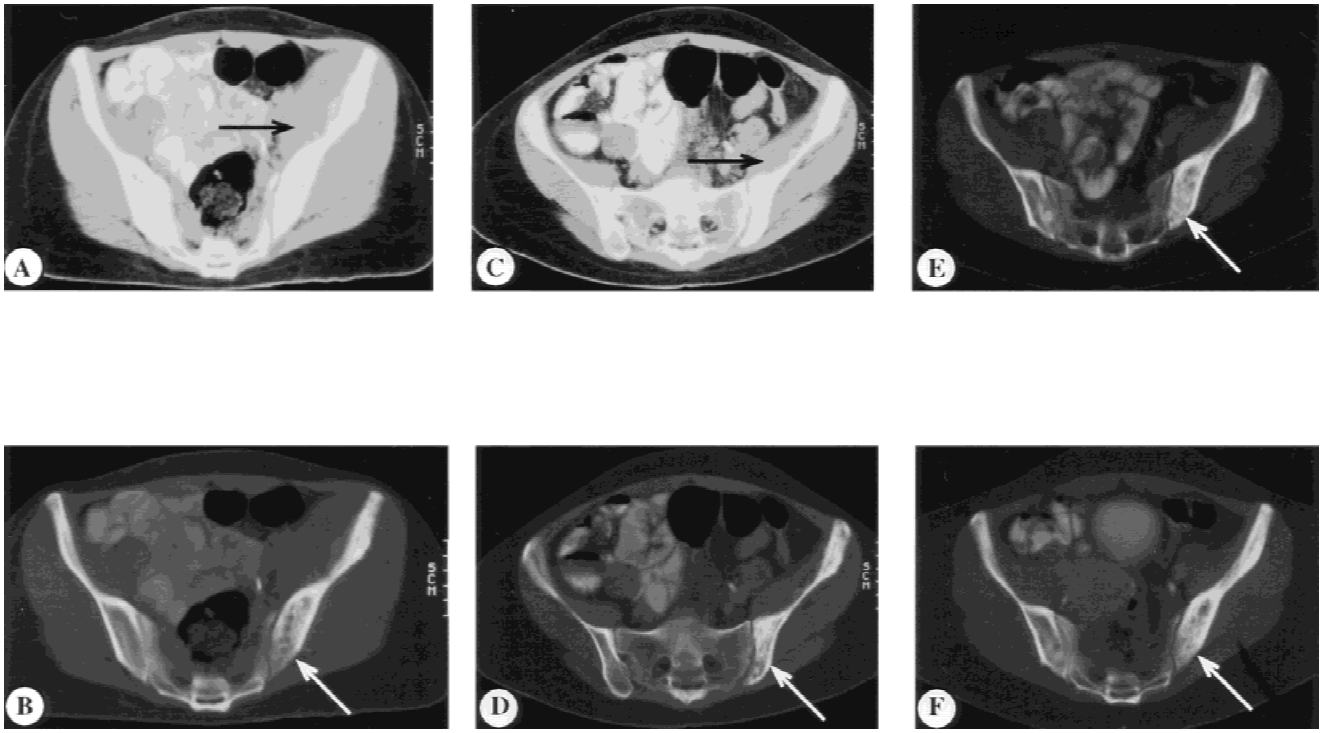

Fig. 2. Computed tomographic images of the pelvic involvement of patient UN-1. Soft tissue (A) and bone windows (B) at diagnosis; Soft tissue (C) and bone windows (D) after three cycles of chemotherapy. Black arrows show regression of the soft tissue abnormality. Images (E) and (F) were taken at 2.2 and 2.8 years, respectively, following the start of treatment. The white arrows show the persistent bone defects.

larly, a study of 37 patients reported that 73% of patients with localized disease had durable survival in contrast to only 9% of patients with disseminated disease [13]. In this study, only two of seven patients with soft tissue invasion survived long term. These studies employed a variety of chemotherapy regimens.

To determine whether the outcome for patients with multifocal, disseminated, or locally invasive bone lymphoma could be improved, nine patients with these clinical features were treated with the ProMACE-CytaBOM regimen. Except for two patients who were >75 years of age at diagnosis, all patients received intensified versions of this regimen. Treatment was well tolerated by all patients except for one who required hospitalization for painful stomatitis. With a median follow-up of 2.3 years, seven patients survived event-free. The 3-year Kaplan-Meier event-free survival for this cohort of patients was 73%. If these data are confirmed in a larger study, randomized trials may be warranted to determine whether intesified versions of the ProMACE-CytaBOM regimen are superior to standard CHOP therapy for patients with large cell lymphoma.

The role of involved-field radiotherapy for patients who receive chemotherapy for bone lymphoma is not clear from this experience. All five patients who received radiotherapy survived event-free while two of four patients who did not receive radiotherapy have relapsed. For patients scheduled to receive radiotherapy to the pelvis, femurs, or to any field that included a large volume of marrow space, pre-radiation stem cell collection was performed to ensure that an optimal product was available in the event that high-dose therapy is needed to treat relapsed disease in the future.

Some authors have suggested a role for osteoclast-inhibiting biphosphonates in the treatment of patients with bone lymphoma. This notion is based on evidence that bone lymphomas may elaborate cytokines such as IL-1β, IL-6, and TNF-α, known to regulate osteoclastic activity [19]. MRI studies of bone lymphoma have demonstrated narrow cortical channels, which correspond to osteoclast-lined tunnels of tumor cells histopathologically. These channels may be an important mechanism for soft tissue extension of bone lymphomas and may explain the frequent absence of extensive cortical destruction in such cases [19].

Interpreting the radiologic follow-up studies for patients who have been treated for bone lymphoma is often challenging. As shown in this report and another [15], follow-up studies can be misleading. While one patient in our series developed early sclerosis in lytic areas consistent with healing (UN-9, data not shown), this patient relapsed shortly after completion of therapy. Stable lytic or lytic/sclerotic lesions were characteristic for patients with ongoing remissions. Adenopathy and soft tissue in-

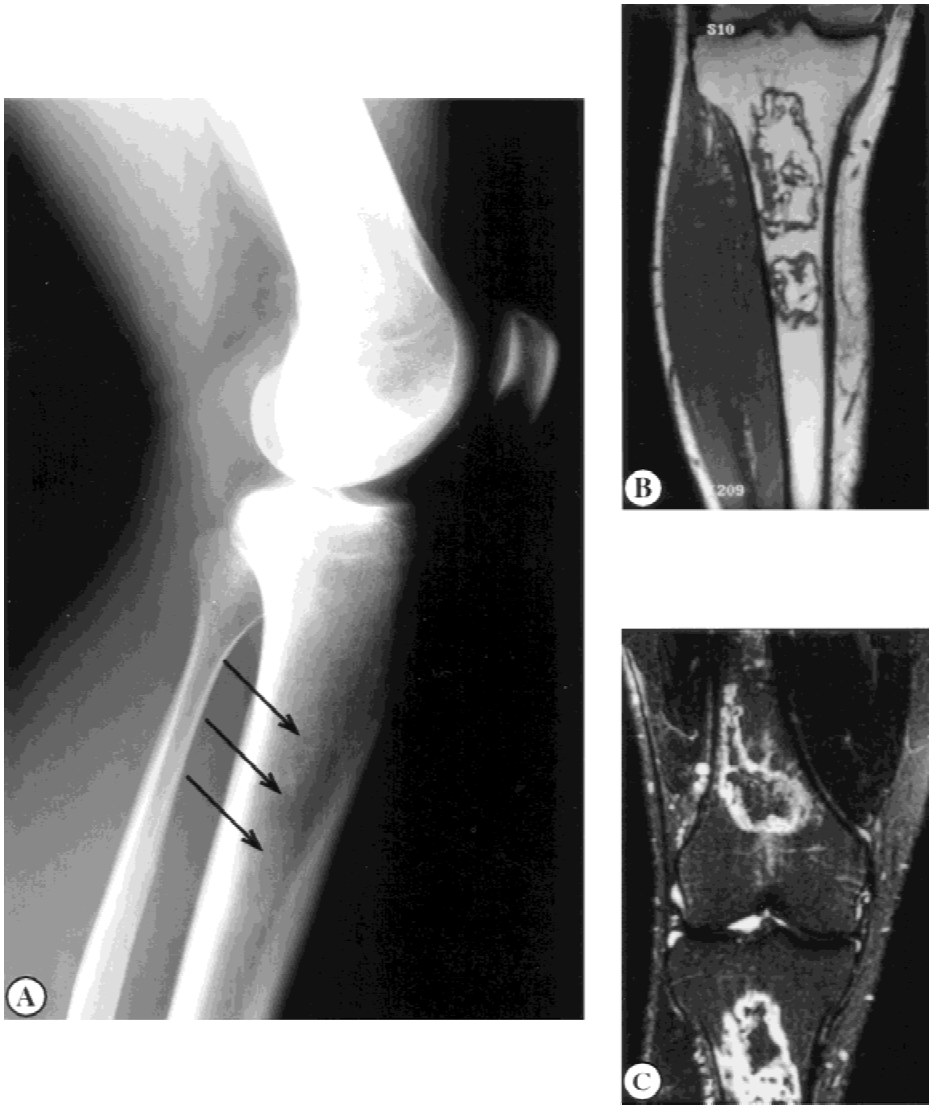

Fig. 3. Multiple infarcts of the distal femur and proximal tibia of patient UN-2. The plain film (A) shows lytic changes (arrows) incorrectly interpreted to be recurrent lymphoma. T1-weighted spin echo MR images (B) show serpiginous lesions with low signal intensity borders characteristic of bone infarcts. On T2-weighted fat suppressed images (C), the borders of the lesions demonstrate high signal intensity compared to the adjacent marrow.

volvement typically resolved in such patients. The persistence of abnormal bone architecture may reflect impaired osseous remodeling due to chemotherapy, radiotherapy, or the original lymphoma. This report also emphasizes that non-malignant processes such as bone infarction may mimic recurrent lymphoma clinically and radiographically.

Non-Hodgkin lymphoma primarily involving bone is an unusual clinical entity. This report shows that patients with multifocal or widespread disease or soft tissue invasion can have prolonged event-free survivals when treated with intensive multi-agent chemotherapy and involved-field radiation. The optimal chemotherapy regimen for these patients remains uncertain and new strategies are needed for patients who develop chemorefractory relapses.

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